Antibiotic Dosing Calculator for Neonates and Children Trial

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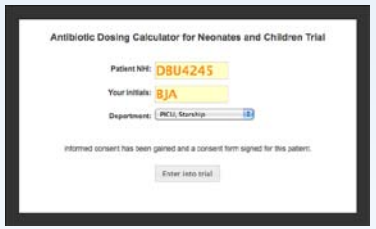
Research question: Does the dosing regimen (loading dose, maintenance dose and dose interval) proposed by the dose calculator result in serum concentrations closer to concentration targets than those achieved by currently used protocols?

Background: A dosing calculator has been developed based on a pharmacokinetic analysis of vancomycin (532 subjects, 1676 concentrations), amikacin (682 subjects, 1717 concentrations) and gentamicin (85 subjects, 1392 concentrations) in premature and full term neonates and infants. The data were collected as part of routine clinical care at sites in Belgium, Portugal, Malaysia and New Zealand. This data set is the largest such data set compiled for these medicines and has been analysed using a principle-based pharmacokinetic model (1-5). The potential benefits of the dosing calculator include improved ability to reach desired drug concentration targets and simpler and less error prone calculation of the dose. Improved targeting of concentration is expected to improve clinical outcomes such as faster resolution of infection and reduced mortality.

Qualification: In order to verify correct operation of the dose calculator system, it has been qualified by making predictions for the hundreds of patients that were used to develop the original model. These predictions have been compared to those made with model development software to ensure the output is equivalent.

A



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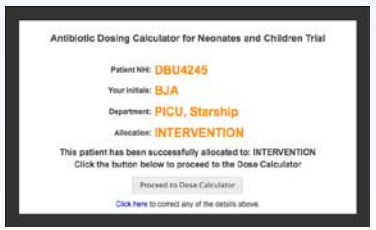

Figure 1. Web-based allocation of patients into trial arms. (A) Initial screen prompting for national health identifier, doctor's initials and department. The NHI is checked in a database and allocated if they have not been already enrolled. (B) A link is provided to the dose calculator if the patient is in the intervention group. Otherwise, a message is displayed instructing to use the current standard of care (department protocol). If the patient has already been allocated, the same group will be shown, preventing duplication.

Figure 2. FirstDose dose calculator running in a web browser. The left panel accepts input of patient covariate values and warns the user with a prompt if the values are out of expected ranges. Input validation is especially important for serum creatinine, which is seldom given units in the clinic. A button at the bottom runs the model, producing a graphical time course in the top right. The calculator looks up the department protocol and displays the protocol regimen, expected time course, peak and trough concentrations. It also proposes a dose regimen that should achieve peak and trough concentrations closer to targets, based on least squares regression. Clicking "Use this regimen" displays a prompt to confirm that the patient will receive the proposed dose. Confirmation is logged in the trial database along with the patient covariate values and output. FirstDose runs in Internet Explorer 6+, Firefox, Chrome, Safari and mobile webkit browsers.

Endpoint: The primary endpoint is how close the measured concentration is to the target concentration. The first set of serum concentrations measured (trough and/or peak) will be compared to the target in each trial arm to see if the dose calculator is effective in reducing this difference. The primary statistical analysis will be a comparison of the mean prediction error in the two groups (conventional vs dose calculator) subsetted according to medicine. Prediction error for each measured concentration is calculated from (Measured – Target)/Target. The Target is the target concentration defined by the middle of the range of concentrations in the treatment protocol for each medicine.

Power: The prediction error using the dosing calculator method has been estimated in a validation data set of 554 vancomycin concentrations measured in neonates and infants (6). The mean prediction error was 1.1% with a standard deviation of 44%. A clinically significant difference in mean prediction error would be 25%. The number of subjects in each arm to be able to reject the null using a two tailed t-test with a power of 80% is 50.

Summary: The Antibiotic Dosing Calculator for Neonates and Children Trial will test if a web-based dosing calculator can achieve target concentrations of gentamicin, amikiacn and vancomycin more reliably than standard protocols in 3 neonatal/paediatric intensive care units. Australia New Zealand Clinical trial Registry ACTRN12610001038088.

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2. Anderson, B. J., K. Allegaert, et al. (2007). "Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance." Br J Clin Pharmacol **63**(1): 75-84.
3. Lo, Y. L., J. G. van Hasselt, et al. (2010). "Population pharmacokinetics of vancomycin in premature malaysian neonates: identification of predictors for dosing determination." Antimicrob Agents Chemother **54**(6): 2626-2632.
4. Sherwin, C. M., E. Kostan, et al. (2009). "Evaluation of the effect of intravenous volume expanders upon the volume of distribution of gentamicin in septic neonates." Biopharm Drug Dispos **30**(5): 276-280.
5. Sherwin, C. M., F. McCaffrey, et al. (2009). "Discrepancies between predicted and observed rates of intravenous gentamicin delivery for neonates." J Pharm Pharmacol **61**(4): 465-471.
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Participants: All admitted patients under the age of 2 years that would ordinarily be treated with gentamicin, amikacin or vancoymcin will be eligible to participate in the trial. Approximately 100 participants will be randomly assigned a trial arm via a website (Figure 1), and the user will be directed to the current standard of care (control) or dose calculator (intervention). Patients in the control group will have their dose regimens decided as they would ordinarily (based on existing protocols or the clinician's judgement). This will involve the covariates: weight, post-menstrual age, post-natal age, gestational age, severe asphyxia status.

Patients in the interventional group will have a dose regimen proposed by the dose calculator. This will involve the clinical staff member entering into the calculator the same details as those in the control group with the addition of covariates: serum creatinine, use of an inotrope, NSAID, or mechanical ventilation, sex, height.

The dose calculator will not use details of asphyxia to propose a dose regimen, but will use the details to look up the regimen based on protocol in order to check if the regimens are similar.

Termination: The study will stop when the anticipated number of patients have been enrolled and evaluated. If some unanticipated major bias in dosing is discovered, after 20 patients, the trial will be stopped.

Exclusion: Patients in the intervention group will receive the dose regimen proposed by the calculator unless:

1. The dose regimen proposed would result in a total dose over 24 hours that differs from the protocol-based dose by more than 50%. If this situation arises, the calculator will display a warning to the user.

or 2. The clinical staff member decides that a different dose regimen should be used for any reason.

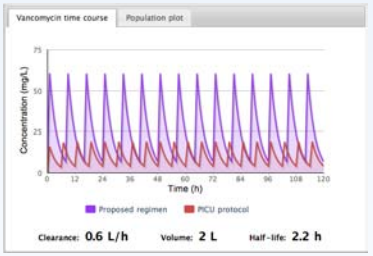

Figure 3. Example showing large differences between the department protocol regimen (30 mg/6 h) and that proposed (131 mg/8 h). This situation would call for exclusion because the proposed regimen calls for 393 mg/24 h while the protocol is only 120 mg/24 h.

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